DETAILED ACTION

Applicant's submission filed on 9/30/2009 has been entered. Claims 1-8, 10, 11 and 15-20 have been cancelled; claims 9 and 12-14 have been amended; no new claims have been added. Claims 9 and 12-14 remain pending in the current application, all of which have been considered on the merits.

All arguments have been fully considered, and will be addressed below, as appropriate. Objections/Rejections not repeated herein have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicants have traversed the rejection of record under 35 USC 112, second paragraph, as being indefinite. The traversal is on the grounds that one having ordinary skill in the art at the time of the invention would consider the subject matter of the claims as being clear and definite in view of the specification. Applicants assert that one having ordinary skill in the art would consider the recited 'further supplements' to include additions to the growth medium, such as proteins, growth factors, lipids and cholesterol.

Applicants' arguments have been fully considered, but are not found persuasive. It is respectfully submitted that Applicants' arguments fail to address the issue that it is not clear what the base "growth medium" consists of, and thus one cannot determine what additives are considered 'supplemental'. Applicants' point that further supplements would correspond to additions to the growth medium actually appears to be in line with the Examiner's interpretation, however if the "growth medium" contains lipids and/or cholesterol (such as in Keen) then these would not be considered "supplements."

Because the claims are directed to the mammalian cell line, per se, and not to the method of adapting a cell line to growth in any particular cell growth medium, the Examiner is unable to suggest allowable language at this time.

Claims 9 and 12-14 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 has been amended to require the mammalian NSO cell line as one which has been adapted for growth in a growth medium that is protein-free, serum-free and free from further supplements. The claim is held indefinite because it is unclear how the growth medium is to be free from 'further supplements', as the base growth medium has not been defined, and thus it cannot readily be determined what is considered 'supplemental.' Growth medium is a heterogenous composition of any number of components, including amino acids, essential nutrients, salts, vitamins, etc; the composition varies based on the source and type. Therefore, it cannot readily be determined what components are considered essential or inherent parts of growth medium, and what components would be considered supplemental. Exclusion of *any* supplements in the growth medium would effectively preclude any nutrient, vitamin, amino acid, etc provided in addition to basic water. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants have traversed the rejection of record under 35 USC 102(b) over Keen et al on the grounds that Keen et al does not teach any of the process steps recited by the instant claims. Applicants cite *Abbott Labs v Sandoz, Inc* 566 F.3d 1282, 90, USPQ2d 1769, which they assert states that "method steps in product-by-process claims now directly limit the scope of the claims with respect to determining patentability of the claims" (Response, Pg. 7). Thus, Applicants assert, because Keen fails to disclose the method of adaptation recited in the claims, it cannot be held to properly anticipate (or render obvious) the instant claims.

Applicants' arguments have been fully considered, the decision in *Abbott Labs v Sandoz, Inc* has also been carefully reviewed; however the arguments are not found persuasive.

First, with regards to the holding of the *Abbotts* case, it is respectfully submitted that the decision in *Abbott* was limited to claim interpretation for infringement purposes. Specifically *Abbott* reads "process terms in product-by-process claims serve as limitations in determining *infringement*" (emphasis added) *See Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 [90 USPQ2d 1769] (Fed. Cir. 2009) (en banc). Analysis for determining infringement of a product-by-process claim is different than that for determining patentability (validity). See *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 92 USPQ2d 1289 (Fed. Cir. 2009), beginning at 1310:.

> "In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it... That is because of the already described, long-standing rule that an old product is not patentable even if it is made by a new process. [footnote: Because validity is determined based on the requirements of patentability, a patent is invalid if a product made by the process recited in a product-by-process claim is anticipated by or obvious from prior art products, even if those prior art products are made by different processes. *Cf. BASF*, 111 U.S. at 311 (assessing the invalidity of an old product recited in a product-by-process claim in terms of patentability).] *As a result, a product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation. In determining infringement of a product-by-process claim, however, the focus is on the process of making the product as much as it is on the product itself.* See *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 [90 USPQ2d 1769] (Fed. Cir. 2009) (en banc). …

> [7] The impact of these different analyses is significant. For product-by-process claims, that which anticipates if earlier does not necessarily infringe if later. That is because a product in the prior art made by a different process can anticipate a product-by-process claim, but an accused product made by a different process cannot infringe a product-by-process claim. Similarly, that which infringes if later does not necessarily anticipate if earlier. That is because an accused product may meet each limitation in a claim, but not possess features imparted by a process limitation that might distinguish the claimed invention from the prior art." (emphasis added)

Therefore, Applicants' argument is not found persuasive, it is maintained that the determination of patentability of a product-by-process claim is based solely on the product, per se, and thus the claims are maintained as properly rejected.

Second, with regards to the argument that the cell line of Keen requires supplementation with insulin, cholesterol and/or lipids, and thus cannot be considered to grow in a protein and serum free medium, completely with out supplements, it is respectfully maintained that it is unclear what is meant by requiring the culture medium to be 'free from further supplements'. In giving the claim its broadest reasonable interpretation, the limitation is interpreted as excluding supplements to the growth medium. However, because the claims do not define the growth medium (beyond serum- and protein-free) the complete growth medium of Keen et al (including WNSA, plus lipids, plus cholesterol and/or plus beta-cyclodextrin (noting that the culture media need not comprise insulin)) still reads on "a growth medium that is protein-free, serum-free and free from further supplements." In order to determine what is and what is not a 'supplement', the base composition must be clearly defined. Any component in growth medium may be considered a supplement, if the base composition is water, or water may even be considered a supplement. Thus, if one interprets the growth medium Keen et al as the fully growth medium in which cells are cultured, then there are no 'further supplements', And the NS0 cells grown by

Keen et al still read on the claimed cells. Thus the rejection under 35 USC 102(b) based on Keen et al is maintained as appropriate.

Claims 9, 12 and 13 stand rejected under 35 U.S.C. 102(b) as being anticipated by Keen et al (Cytotechnology, 1996).

Applicants' amended claims are directed to a mammalian NS0 cell line adapted to growth in a serum- and protein-free media. Dependent claims require the NS0 cells to contain sequences encoding for recombinant polypeptides or proteins, more specifically recombinant antibodies or fragments thereof. The claims are determined to be product-by-process claims, the process limitations being directed to an adaptation method for adapting the cells to protein-free conditions. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, unless the method of production imparts a unique structural feature to the product. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case the method of adaptation to survival protein-free culture does not affect the cell line, per se, as the method does not impart any patentable distinctions to the cell line. Therefore, any mammalian NS0 cell line adapted to growth in serum- and protein-free media, with the claimed characteristics, anticipates the claims.

Keen et al disclose GS-engineered NS0 cell lines adapted to grow in serum-free and protein-free media (See Keen et al, abstract). Please note the media used by Keen et al is considered 'free from further supplements' because all components present in the medium are considered part of the growth medium. Keen et al culture NS0 9D4.5A 11 (9D4) cells, NS0 2H5 cells (2H5), and NS0 8C9.50B5 (8C9) cells; 9D4 and 2H5 cells express CAMPATH-1H antibodies, and 8C9 cells express humanized anti-CD2 antibody (See Keen et al, Pg. 209, col. 1 and Pg 210, col. 2-Pg. 212, col. 2). Each of the cell lines therefore contain sequences encoding for recombinant antibodies.

Reference is particularly made to Figure 1. Figure 1 compares cell growth in WNSA protein-free media, supplemented with *either* 1. lipid, beta-cyclodextrin and recombinant insulin, 2. lipids with extra ribonucleotide; 3. lipids with extra glutamic acid and asparagine; or 4. lipids with extra glutamic acid, asparagine, and ribonucleotides. Highest cell growth and antibody production was achieved with medium 4- which does not contain insulin or other proteins. (See Pg. 213, col. 1 and Fig. 1). Therefore, each of the NS0 9D4, 2H5 and 8C9 cells were capable of growing in completely serum- and protein-free media, and thus meet the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicants have traversed the rejections under 35 USC 103(a) on the grounds that the Office has not established a *prima facie* case of obviousness because Keen et al does not disclose each and every limitation of the current claims, and the secondary references do no remedy this deficiency. Specifically, Applicants assert the artisan of ordinary skill would not regard claim 9 as obvious in view of the combination of the references, as cited references do not disclose or suggest any apparent reason or other rationale to modify the applied art to correspond with the subject matter of claim 9.

In response, the arguments as to Keen et al have been addressed above. Keen et al is maintained as an appropriate grounds of rejection. Absent specific arguments as to the combination of references as they relate to the subject matter of claim 14, the rejection under 35 USC 103(a) is also maintained as appropriate.

Claims 9 and 12-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Keen et al (Cytotechnology, 1996), in view of Crombet-Ramos et al (Int. J. Cancer, 2002, published online 27 August 2002).

Applicants' amended claims are directed to a mammalian NS0 cell line adapted to growth in a serum- and protein-free media. Dependent claims require the NS0 cells to contain sequences encoding for recombinant polypeptides or proteins, more specifically recombinant antibodies or fragments thereof, and more specifically the humanized recombinant antibody anti-EGF-R hR3 or a fragment thereof. The claims are determined to be product-by-process claims, the process limitations being directed to an adaptation method for adapting the cells to protein-free conditions. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, unless the method of production imparts a unique structural feature to the product. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case the method of adaptation to survival protein-free culture does not affect the cell line, per se, as the method does not impart any patentable distinctions to the cell line. Therefore, any mammalian NS0 cell line adapted to growth in serum- and protein-free media, with the claimed characteristics, anticipates the claims.

Keen et al disclose NS0 cell lines which are adapted to grow in serum- and protein-free media (See Keen et al, abstract). Keen et al states that production of antibodies and therapeutic proteins in fully defined (serum- and protein-free) media is desirable due to lower cost, better reproducibility, regulatory considerations and purification of the product (See Keen et al, Pg. 208, third full paragraph). Keen et al disclose NS0 9D4.5A 11 (9D4) cells, NS0 2H5 cells (2H5), and NS0 8C9.50B5 (8C9) cells; 9D4 and 2H5 cells express CAMPATH-1H antibodies, and 8C9 cells express humanized anti-CD2 antibody (See Keen et al, Pg. 209, col. 1 and Pg 210, col. 2-Pg. 212, col. 2). Keen et al do not disclose NS0 cells which product a humanized anti-EGFR antibody hR3.

At the time the invention was made, the humanized anti-EGFR antibody hR3 was recognized as a potential anti-cancer agent (See Crombet-Ramos et al, abstract), and thus production of this antibody was desirable.

Because production of humanized anti-EGFR antibody hR3 was recognized as desirable, it would thus have been obvious to one of ordinary skill in the art to use the method of Keen et al to create NS0 cells engineered to produce humanized anti-EGFR antibody hR3, wherein the cells are adapted to grow in serum- and protein-free media.

One would have had a reasonable expectation of successfully engineering the NS0 cells to encode for the anti-EGFR antibody hR3 because the coding sequence for the anti-EGFR antibody hR3 was known in the art (See Crombet-Ramos et al), and because methods of engineering NS0 cells to encode for any desired sequence, as well as methods of adapting NS0 cells to growth in serum- and protein-free conditions were known in the art (See Keen et al). Thus, it would have been within the technical grasp of the artisan of ordinary skill to transduce NS0 cells to encode for the anti-EGFR antibody hR3 coding sequence, and then to subject those cells to the method of Keen et al, wherein the cells are adapted to serum- and protein-free growth to produce the transduced protein sequence. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651